PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

ASTRAZENECA
Global Intellectual Property
S-151 85 Sodertalje
SUEDE

CODE	DATE	NTD

ANKOM 18 JAN 2006 GIPS

DATA ENTERED

FINAL CHECK EHJ

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)* 16.01.2006

Applicant's or agent's file reference
101319-1 WO

IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/005337	20.12.2004	24.12.2003 19 JAN 2006

Applicant
ASTRAZENECA AB et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
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Authorized Officer

Ambroa, J.R.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

CODE	DATE	NTD
ANKOM	18 JAN 2006	GIPS
DATA ENTERED		
FINAL CHECK		

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
101319-1 WO		

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/005337	20.12.2004	24.12.2003

International Patent Classification (IPC) or national classification and IPC
A61K31/505, C07D239/42, A61P35/00, C07D405/12, C07D417/12, C07D413/12, C07D401/12, C07D413/14, C07D401/06, C07D417/06, C07D403/12

Applicant
ASTRAZENECA AB et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 12 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23.09.2005	16.01.2006

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Seymour, L Telephone No. +49 89 2399-8694

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/005337

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-163 as originally filed

   Claims, Numbers

   1-16 received on 11.11.2005 with letter of 09.11.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/005337

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 16 (part)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. as above

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/005337

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-16
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Present claim 16 relates to compounds defined by reference to process claim 15 in which it is stated that "any functional group is protected if necessary", and Lg^2 and Lg^3 are defined as "a suitable displaceable group". Whereas these terms are considered to be clear in the context of the particular reaction claimed, they lead to a lack of clarity (Article 6 PCT) in the compound claims, divorced from the corresponding reaction conditions. It is thus unclear which specific compounds fall within the scope of said claim. Consequently, the search of claim 16 did not include compounds wherein "any functional group is protected if necessary", and the meanings of Lg^2 and Lg^3 were restricted to the specific leaving groups listed as preferred embodiments in claim 15 as originally filed.

The opinion expressed below with regard to novelty, inventive step and industrial applicability refers only to subject-matter for which an international search report has been drawn up.

Re Item V

1. Reference is made to the following documents:

   D1: WO 03/029209 A
   D2: WO 03/080625 A
   D3: WO 02/08205 A

2. The present application meets the criteria of Article 33(1) PCT:

   The present compounds differ from those of D1 and D2 in the replacement of the five-membered ring fused to the pyrimidinyl ring with an ethynyl linker.

   With the restriction in the meaning of A in claim 16 such that it can no longer be aryl, novelty has been restored with respect to D3.

3. Claims 1-16 meet the requirements of the PCT with respect to inventive step (Article 33(3) PCT):

The problem underlying the present application lies in the provision of further compounds having inhibitory activity for the Tie2 receptor tyrosine kinase and accordingly having value in the treatment of disease states associated with pathological angiogenesis.

Documents D1 and D2 disclose compounds having the same activity as the present compounds, where the main difference in structure lies in the replacement of the five-membered ring fused to the pyrimidinyl ring in D1 and D2 with an ethynyl linker. No incentive is provided in the prior art that would lead the person skilled in the art to perform this modification as a solution to the above-mentioned problem. It has been made credible that the claimed compounds solve the present problem (see present description, p. 85).

The intermediates of claim 16 are considered to bring to the present compounds of formula I the structural element which makes the contribution over the prior art and are therefore patentable with the patentable end compounds of claim 1.

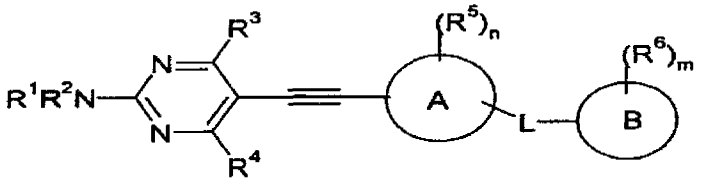
Re Item VIII

1. Claim 16 is unclear because the compounds are defined by reference to process claim 15 containing functional definitions which are clear within the context of the process but not in the context of an independent compound claim (cf. Item III). It is also noted that the point of attachment of L (*meta* or *para*) is implicit in claim 15 (through the reference to claim 1), but is not clearly specified in claim 16, particularly for intermediate VIc.

2. Claim 10 is unclear (Article 6 PCT) owing to its reference to the description (see also Rule 6.2(a) PCT).

CLAIMS

1. A compound of the Formula I:



Formula I

wherein:

R^1 and R^2 are independently selected from hydrogen, (1-6C)alkylsulfonyl, phenyl$(CH_2)_u$- wherein u is 0, 1, 2, 3, 4, 5 or 6, (1-6C)alkanoyl, (1-6C)alkyl, (1-6C)alkoxycarbonyl, (3-6C)cycloalkyl$(CH_2)_x$- in which x is 0, 1, 2, 3, 4, 5 or 6, or a 5 or 6 membered heteroaryl ring, or **R^1 and R^2** together with the nitrogen atom to which they are attached represent a saturated or partially saturated 3 to 7 membered heterocyclic ring optionally containing another hetero atom selected from N or O;

wherein the (1-6C)alkyl, the (1-6C)alkanoyl and the (3-6C)cycloalkyl groups are optionally substituted by one or more groups independently selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy(1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, mono(1-6C)alkylcarbamoyl, di-[(1-6C)alkyl]carbamoyl, $-N(R^d)C(O)$(1-6C)alkyl in which R^d is hydrogen or (1-6C)alkyl, a saturated or partially saturated 3 to 7 membered heterocyclic ring, or a 5 or 6 membered heteroaryl ring,

wherein the (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy and (1-6C)alkoxy(1-6C)alkoxy(1-6C)alkoxy groups and the (1-6C)alkyl groups of the mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, mono(1-6C)alkylcarbamoyl, di-[(1-6C)alkyl]carbamoyl and/or $-N(R^d)C(O)$(1-6C)alkyl groups are optionally substituted by one or more hydroxy groups;

wherein the phenyl is optionally substituted by one or more groups independently selected from halo, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, wherein the (1-6C)alkyl and the (1-6C)alkoxy

groups are optionally substituted by one or more groups independently selected from hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino;

and wherein any heterocyclic and heteroaryl rings within R^1 and/or R^2 are optionally independently substituted by one or more of the following: (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, a saturated or partially saturated 3 to 7 membered heterocyclic ring or $-C(O)(CH_2)_zY$ wherein z is 0, 1, 2 or 3 and Y is selected from hydrogen, hydroxy, (1-4C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

and provided that when R^1 and/or R^2 is a (1C)alkanoyl group, then the (1C)alkanoyl is not substituted by fluoro or hydroxy;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl or (1-6C)alkoxy, wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups independently selected from: fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, mono(1-6C)alkylcarbamoyl or di-[(1-6C)alkyl]carbamoyl, a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein said heterocyclic and heteroaryl rings are optionally independently substituted by one or more of the following: (1-4C)alkyl, (1-4C)alkoxy, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

or one of **R^3** and **R^4** is as defined above and the other represents a group **$-NR^1R^2$** as defined above;

A represents an aryl group or a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazinyl;

R^5 is selected from cyclopropyl, cyano, halo, (1-6C)alkoxy or (1-6C)alkyl, wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by cyano or by one or more fluoro;

n is 0, 1, 2 or 3;

L is attached meta or para on ring A with respect to the point of attachment of the ethynyl group and represents $-C(R^aR^b)C(O)N(R^9)-$, $-N(R^8)C(O)C(R^aR^b)-$, $-N(R^8)C(O)N(R^9)-$, $-N(R^8)C(O)O-$, or $-OC(O)-N(R^9)-$, wherein R^8 and R^9 independently represent hydrogen or (1-6C)alkyl and wherein R^a and R^b independently represent hydrogen or (1-6C)alkyl or R^a and R^b together with the carbon atom to which they are attached represent (3-6C)cycloalkyl;

B represents a (3-7C)cycloalkyl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring, an aryl group, a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazinyl, or a 8, 9 or 10 membered bicyclic group which optionally contains 1, 2, 3 or 4 heteroatoms independently selected from N, O and S and which is saturated, partially saturated or aromatic;

R^6 is selected from halo, cyano, oxo, a (3-7C)cycloalkyl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring, and $-N(R^c)C(O)$(1-6C)alkyl in which R^c is hydrogen or (1-6C)alkyl; or

R^6 is selected from (1-6C)alkyl, $-S(O)_p$-(1-6C)alkyl wherein p is 0, 1 or 2, or (1-6C)alkoxy, wherein the (1-6C)alkyl, $-S(O)_p$-(1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups independently selected from cyano, fluoro, hydroxy, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, a (3-7C)cycloalkyl ring or a saturated or partially saturated 3 to 7 membered heterocyclic ring; and

wherein the (3-7C)cycloalkyl ring and saturated or partially saturated 3 to 7 membered heterocyclic ring are optionally independently substituted by one or more groups selected from (1-6C)alkyl; and

m is 0, 1, 2 or 3;

and when B is a (3-7C)cycloalkyl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring or a saturated or partially saturated 8, 9 or 10 membered bicyclic group, the rings and the bicyclic group optionally bear 1 or 2 oxo or thioxo substituents;

and salts thereof.

2. A compound of Formula I according to Claim 1, wherein:

R^6 is selected from halo, cyano, a (3-7C)cycloalkyl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring or an alkanoylamino group $-N(R^c)C(O)$(1-6C)alkyl in which R^c is hydrogen or (1-6C)alkyl; or

R^6 is selected from (1-6C)alkyl or (1-6C)alkoxy, wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups independently selected from cyano, fluoro, hydroxy, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, a (3-7C)cycloalkyl ring or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

and salts thereof.

3. A compound of the Formula I according to claim 1, wherein:

R^1 and R^2 are independently selected from hydrogen, (1-6C)alkylsulfonyl, phenyl$(CH_2)_u$- wherein u is 0, 1, 2, 3, 4, 5 or 6, (1-6C)alkanoyl, (1-6C)alkyl, (1-6C)alkoxycarbonyl, or (3-6C)cycloalkyl$(CH_2)_x$- in which x is 0, 1, 2, 3, 4, 5 or 6 or R^1 and R^2 together with the nitrogen atom to which they are attached represent a saturated or partially saturated 3 to 7 membered heterocyclic ring optionally containing another hetero atom selected from N or O;

wherein the alkyl and the cycloalkyl groups are optionally substituted by one or more groups selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, a saturated or partially

saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein said heterocyclic and heteroaryl rings are optionally independently substituted by one or more of the following: (1-4C)alkyl, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

and wherein the phenyl is optionally substituted by one or more groups selected from halo, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, wherein the (1-6C)alkyl or (1-6C)alkoxy are optionally substituted by hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl or (1-6C)alkoxy wherein the alkyl and the alkoxy groups are optionally substituted by one or more groups selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein said heterocyclic and heteroaryl rings are optionally independently substituted by one or more of the following: (1-4C)alkyl, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

or one of R^3 and R^4 is as defined above and the other represents a group $-NR^1R^2$ as defined above;

R^5 is selected from cyano, halo, (1-6C)alkoxy or (1-6C)alkyl optionally substituted by cyano or by one or more fluoro;

B represents a (3-7C)cycloalkyl ring, an aryl or a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazinyl;

R^6 is selected from halo, cyano, a saturated or partially saturated 3 to 7 membered heterocyclic ring or an alkanoylamino group $-N(R^c)C(O)$(1-6C)alkyl in which R^c is

hydrogen or (1-6C)alkyl; or R^6 is selected from (1-6C)alkyl or (1-6C)alkoxy, wherein the alkyl and the alkoxy groups are optionally substituted by one or more groups selected from cyano, fluoro, hydroxy, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, or a saturated or partially saturated 3 to 7 membered heterocyclic ring; and

m is 0, 1, 2 or 3; and when m is at least 2 then two substituents on adjacent carbon atoms in ring B may together represent a methylenedioxy group;

and wherein A, L and n are as defined in Claim 1.
and salts thereof.

4. A compound according to any one of Claims 1, 2 and 3 wherein A is selected from phenyl, pyridyl, thiazolyl, thiadiazolyl or pyrimidinyl.

5. A compound accordingly to any one of the preceding claims wherein B is selected from phenyl, 2,3-di-hydro-indenyl, piperidinyl, pyridyl, pyrazolyl, isothiazolyl, thiadiazolyl, isoxazolyl, benzodioxinyl, benzodioxolyl or tetrahydropyranyl

6. A compound accordingly to any one of the preceding claims wherein L is selected from $-N(R^8)C(O)N(R^9)-$, $-N(R^8)C(O)O-$ or $-N(R^8)C(O)CH_2-$ wherein R^8 and R^9 independently represent hydrogen or (1-6C)alkyl.

7. A compound accordingly to any one of the preceding claims wherein R^1 and R^2 are both hydrogen or R^1 is hydrogen or (1-6C)alkyl and R^2 is (1-6C)alkyl
wherein (1-6Calkyl) is optionally substituted by hydroxy, amino, mono(1-6C)alkylamino or di(1-6C)alkylamino, carbamoyl, (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, $-N(R^d)C(O)$(1-6C)alkyl in which R^d is hydrogen or (1-6C)alkyl, aryl (particularily phenyl), a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring;
wherein the (1-6C)alkoxy, mono(1-6C)alkylamino and $-N(R^d)C(O)$(1-6C)alkyl groups are optionally substituted by hydroxy;

wherein an aryl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring is optionally substituted by (1-4C)alkyl, (1-4C)alkoxy or $-C(O)CH_2Y$ wherein Y is selected from hydroxy or di(1-6C)alkylamino.

8. A compound accordingly to any one of the preceding claims wherein R^3 and R^4 are both hydrogen.

9. A compound accordingly to any one of the preceding claims wherein R^6 is independently selected from halo, cyano, oxo, (3-7C)cycloalkyl, a saturated 3 to 7 membered heterocyclic ring (optionally substituted by (1-4C)alkyl), $-N(R^c)C(O)$(1-6C)alkyl wherein R^c is hydrogen or (1-6C)alkyl (particularly (1-4C)alkyl), (1-6C)alkyl (optionally substituted by up to three groups independently selected from halo) or (1-6C)alkoxy and m is selected from 1 or 2.

10. A compound according to Claim 1 which is any one or more of examples 1 to 152 or a salt thereof.

11. A pharmaceutical composition which comprises a compound of the Formula I, or a pharmaceutically acceptable salt thereof, as defined in claims 1 to 10 in association with a pharmaceutically acceptable diluent or carrier.

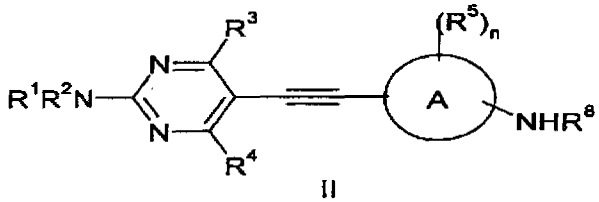
12. A compound of the Formula I, or a pharmaceutically acceptable salt thereof, as defined in claims 1 to 10, for use as a medicament.

13. Use of a compound of the Formula I, or a pharmaceutically acceptable salt thereof, as defined in claims 1 to 10, in the manufacture of a medicament for use as a Tie2 receptor tyrosine kinase inhibitor in a warm-blooded animal such as man.

14. Use of a compound of the Formula I, or a pharmaceutically acceptable salt thereof, as defined in claims 1 to 10, in the manufacture of a medicament for use in the production of an anti-angiogenic effect in a warm-blooded animal such as man.

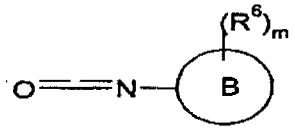
15. A process for preparing a compound of formula I, or salt thereof, as defined in Claim 1, or a pharmaceutically acceptable salt thereof (wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} L , ring A and ring B, n and m are, unless otherwise specified, as defined in Claim 1) comprising:

(a) For compounds of the formula I wherein L is $-N(R^8)C(O)N(H)-$, the reaction of a compound of the formula II:



II

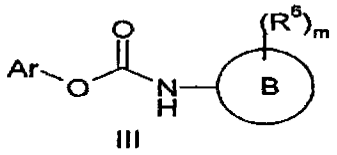
wherein R^1, R^2, R^3, R^4, R^5, R^8, n and A have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an isocyanate of the formula IV:



IV

wherein R^6, m and B have any of the meanings defined hereinbefore except that any functional group is protected if necessary; or

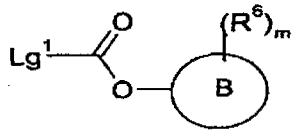
(b) For compounds of the formula I wherein L is $-N(R^8)C(O)N(H)-$, the reaction of a compound of the formula II as defined above with an aryl carbamate of the formula III:



III

wherein Ar is a suitable aryl group and R^6, m and B have any of the meanings defined hereinbefore except that any functional group is protected if necessary; or

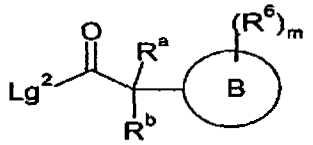
(c) For compounds of the formula I wherein L is $N(R^8)C(O)-O-$, the reaction of a compound of the formula II as defined above with a compound of the formula XI:



XI

wherein Lg^1 is a suitable displaceable group and R^6, m and B have any of the meanings defined hereinbefore except that any functional group is protected if necessary; or

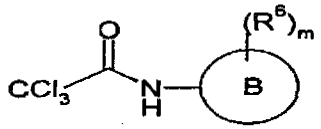
(d) For compounds of the formula I wherein L is $N(R^8)C(O)C(R^aR^b)$, the reaction of a compound of the formula II as defined above with a compound of the formula IX:



IX

wherein Lg^2 is a suitable displaceable group, R^x-C(O)-O- or R^x-O- (wherein R^x is a suitable alkyl or aryl group) and R^6, R^a, R^b, m and B have any of the meanings defined hereinbefore except that any functional group is protected if necessary; or

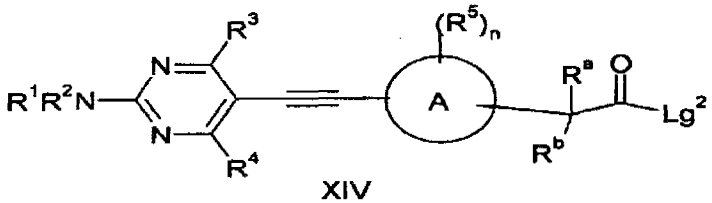
(e) For compounds of the formula I wherein L is $-N(R^8)C(O)N(H)-$, the reaction of a compound of the formula II as defined above with a trichloroacetylamine of the formula XIII:



XIII

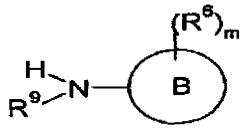
wherein R^6, m and B have any of the meanings defined hereinbefore except that any functional group is protected if necessary; or

(f) For compounds of the formula I wherein L is $-C(R^aR^b)C(O)N(R^9)-$, the reaction of a compound of the formula XIV:



XIV

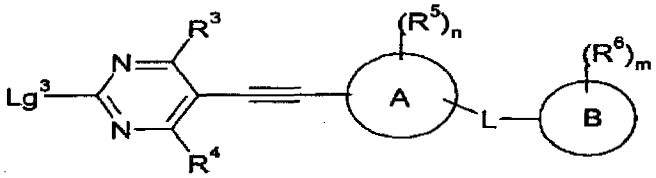
wherein Lg^2 is a suitable displaceable group as described above and R^1, R^2, R^3, R^4, R^5, R^a, R^b, n and A have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an amine of the formula XV:



XV

wherein R^6, R^9, m and B have any of the meanings defined hereinbefore except that any functional group is protected if necessary; or

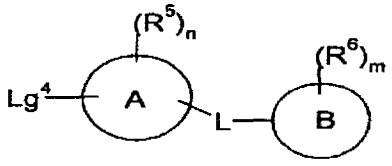
(g) The reaction of a compound of the formula XVI:



XVI

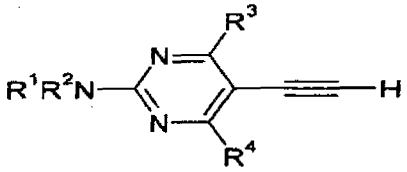
wherein Lg^3 is a suitable displaceable group, methyl sulfonyl, methylthio or aryloxy and R^3, R^4, R^5, R^6, n, m, A, B and L have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an amine of the formula HNR^1R^2, wherein R^1 and R^2 have any of the meanings defined hereinbefore except that any functional group is protected if necessary; or

(h) The reaction of a compound of the formula XVII:



XVII

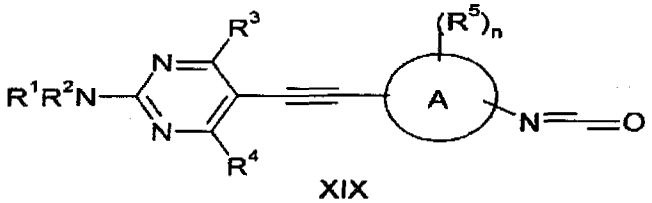
wherein Lg^4 is a suitable displaceable group or a sulfonyloxy group and R^5, R^6, n, m, A, B and L have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an alkyne of the formula XVIII:



XVIII

wherein R^1, R^2, R^3 and R^4 have any of the meanings defined hereinbefore except that any functional group is protected if necessary; or

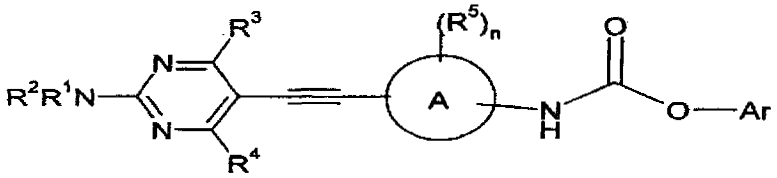
(i) For compounds of the formula I wherein L is $-N(H)C(O)N(R^9)-$, the reaction of an isocyanate of the formula XIX:



XIX

wherein R^1, R^2, R^3, R^4, R^5, n and A have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an amine of the formula XV as defined above; or

(j) For compounds of the formula I wherein L is $-N(H)C(O)N(R^9)-$, the reaction of a compound of the formula XX:



XX

wherein Ar is a suitable aryl group and R^1, R^2, R^3, R^4, R^5, n and A have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an amine of the formula XV as defined above.

and thereafter if necessary:

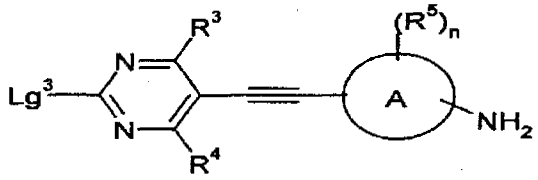
i) converting a compound of the Formula (I) into another compound of the Formula (I);

ii) removing any protecting groups;

iii) forming a salt.

16. A compound selected from Formulae II, XIV, XVI, XIX and XX as defined in Claim 15, wherein A is a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazinyl

or a compound of Formula VIc:



VIc

or salt thereof, wherein A is a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazinyl and Lg3, R^3, R^4, R^5 and n are as defined in Claim 15.